REMARKS

I. Status of the claims

Claims 16, 20-25, 30-35 and 71-93 are pending in this application. Claims 16, 30 and 35 have been amended. New claim 71 has been added to affirmatively recite the administration of another antihypertensive, a cholesterol lowering agent, a diuretic or aspirin to the patient, which was recited as optional in the method of claim 16. New claims 72-73 recite administering ramipril and ramiprilat, respectively. Claims 74-76 recite individual cardiovascular events that have also been added to claim 16 from canceled claim 17.

Claim 18 has been canceled and re-written in independent form as new claim 77. Canceled claim 19, which depended from claim 18, is now new claim 78. Claims 79-93 depend either directly or indirectly from claim 77, and recite subject matter that corresponds to claims that depend from claim 16.

II. Restriction requirement and election of species

Claims 19, 29 and 35-70 have been withdrawn from consideration. Applicants have canceled claims 29 and 36-70 and respectfully request that the Examiner reconsider the withdrawal from consideration the subject matter of claims 19 (now claim 78) and 35. Claim 19 (now claim 78) depended from claim 18 (now claim 77), which was examined, and specified the type of revascularization procedure recited in claim 18. Claim 35 depends from claim 16, which was also being examined, and recites the further administration of a calcium channel blocker or a beta blocker to the patient. Assuming that claims 16 and 77 will ultimately be found allowable, claims 78 and 35 should also be allowable because they incorporate all limitations of claim 77 and 16, respectively. As a result, it should not present a serious burden to examine the subject matter of claims 78 and 35 with the remaining claims of the application. Applicants therefore respectfully request that all claims now pending in the application be examined together.

III. Objection to the specification

The Examiner objected to the disclosure, requiring applicants to indicate that the parent application has been abandoned. Applicants have made the requested amendment.

IV. Rejection under 35 U.S.C. § 112, first paragraph

Claims 16-18, 20-28 and 30-34 were rejected under 35 U.S.C. § 112, first paragraph as not being enabled for the prevention of the risk of a cardiovascular event. The Examiner also indicated that the term "preventing" itself was not enabled.

The text of the rejected claims was not intended to recite "preventing the risk" of a cardiovascular event. The claims were intended to recite the prevention of a cardiovascular event or reducing the risk of a cardiovascular event. Claim 16 has been amended to recite a method for reducing the risk of a cardiovascular event. Claim 77 has also been written the same way. As mentioned on page 3 of the Office Action, the application disclosure enables the subject matter now claimed. Applicants therefore respectfully request that the Examiner withdraw this rejection.

V. Rejection under 35 U.S.C. § 103(a)

Claims 16-18, 20-28 and 30-34 were rejected under 35 U.S.C. § 103(a) as being unpatentable in view of U.S. Patent No. 5,622,985 to Olukotun et al. ("Olukotun") in view of the Merck Manual and the disclosure at page 6, last paragraph to page 7, second full paragraph of the application. In support of the rejection, the Examiner stated that Olukotun teaches a method of preventing or reducing the risk of a second heart attack, which comprises administering to a patient in need thereof a combination of a statin with an angiotensin converting enzyme ("ACE") inhibitor such as ramipril. The Examiner characterized the differences between the invention and the prior art as being the presence in the claims of patient risk factors or diabetes or age and specific types of ACE inhibitors. The Examiner concluded that the disclosure of risk factors in the Merck Manual and the reference to known ACE inhibitors in the application rendered the invention obvious.

Applicants respectfully traverse this rejection. Claim 16, the only independent claim now pending, recites a method for reducing the risk of a cardiovascular event in a patient with an increased cardiovascular risk and no evidence of left ventricular dysfunction. In order to establish a *prima facie* case of obviousness of this claim and all others, the

Examiner must show, among other things, that one skilled in the art would have had a reasonable expectation of success in carrying out that method. *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Moreover, there must be a teaching or suggestion from the prior art of all the claim limitations. MPEP § 2143. As explained below, however, the cited references do not teach all limitations of the claims and one skilled in the art would not have had a reasonable expectation of success in practicing the claimed invention.

The Olukotun patent discloses a method for preventing the onset of or reducing the risk of onset of a second heart attack in a mammal having a substantially normal serum cholesterol level with an HMG CoA reductase inhibitor alone or in combination with an ACE inhibitor. Olukotun at col. 2, line 65 to col. 3, line 5. Nowhere does Olukotun inherently or explicitly teach or suggest that the patient population is or may be one having no evidence of left ventricular dysfunction as recited in claim 16. The secondary references do not supply this teaching either. For at least this reason, the cited references fail to create a *prima facie* case of obviousness of the invention.

Regarding the element of expectation of success, the prior art as a whole reflected a belief that ACE inhibitors brought about their beneficial effects through their action on functionally impaired cardiac muscle. A patient having no evidence of left ventricular dysfunction would not suffer from such impairment of the cardiac muscle. As a result, there would have been no reasonable basis to expect success in reducing the risk of a cardiovascular event with the ACE inhibitors ramipril or ramiprilat in that patient. A number of clinical trials, and commentaries on those trials, support this interpretation of the state of the art. It is appropriate for applicants to refer to these other studies to illustrate that Olukotun, when read in context of other art, did not provide the necessary reasonable expectation of success to practice the claimed invention. *See, e.g., In re Dow Chem. Co.*, 5 U.S.P.Q.2d at 1532.

Investigators had previously conducted a "Prevention Trial" and "Treatment Trial" of heart failure as part of the Studies of Left Ventricular Dysfunction ("SOLVD") with the ACE inhibitor enalapril. As the names of the studies imply, the patients in those trials had left ventricular dysfunction, evidenced by an ejection fraction of 0.35 or less. In a summary of the "Prevention Trial," the investigators observed "a significant trend toward <u>less benefit from enalapril among patients with a higher ejection fraction</u>" and that "[t]he benefits of

enalapril in preventing heart failure and hospitalization were greatest among the patients with the lowest ejection fraction" (underlining added).[1,2] The investigators noted a similar trend of "lesser benefit among patients with higher ejection fractions" in the Treatment Trial as well. *Id.*

The observation of lesser benefit for patients with higher ejection fractions would not have given one skilled in the art a reasonable expectation of success in expanding the patient population to those having higher ejection fractions and who demonstrate no evidence of left ventricular dysfunction. The investigators of the SOLVD Prevention Trial themselves recommended "that caution be exercised in extrapolating the results of the SOLVD trials to patients with ejection fractions above 0.35." *Id.* A review article that evaluated the results of the SOLVD trials as well as the SAVE trial (studying the effects of the ACE inhibitor captopril on patients with ejection fractions of 0.40 or less) also counseled against extrapolating the results of the studies:

> Given a tendency towards less benefit in those with lower degrees of LV [left ventricular] dysfunction seen in the SOLVD and SAVE Trials, it would not be prudent to extrapolate the results of these trials to patients with ejection fractions over 40%. Although it appears that the anti-ischaemic effect of ACE inhibitors could potentially be extrapolated to those with relatively preserved left ventricular function, this hypothesis requires verification in prospectively designed studies (underlining added).[3]

Applicants are aware that "absolute predictability" of success is not required to sustain an obviousness rejection, but what is needed instead is a "reasonable expectation" of success. In this field, however, authors of the publications cited above expressly declined to predict success of effects of ACE inhibitors in a patient population that has no

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[1] The SOLVD Investigators, "Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fractions," The New England Journal of Medicine, vol. 327, no. 10, pp. 685-691 at p. 689, col. 1 and page 690, col. 2 (1992).

[2] Most articles cited in this Amendment have been submitted in Information Disclosure Statements. Applicants nonetheless enclose additional courtesy copies of the documents for the Examiner's reference. A copy of an additional document, authored by the PEACE Investigators, is enclosed in an Information Disclosure Statement filed together with this Amendment.

[3] McKelvie et al., "Role of angiotensin converting enzyme inhibitors in patients with left ventricular dysfunction and congestive heart failure," European Heart Journal, vol. 15 (Supp. B), pp. 9-13 at 12-13 (1994).

evidence of left ventricular dysfunction based on results on patients that do have left ventricular dysfunction. The authors' comments also reflect that, at least in the context of this field of medicine, direct proof of successful results in the new patient population was required:

> The evidence provided by the SOLVD and SAVE trials suggests the intriguing possibility that the reduction in ischemic events may occur in a broader group of high-risk patients such as those with preserved left ventricular ejection fraction. However, such patients may not have significant increases in the systemic levels of renin and angiotensin, although activation of the local tissue angiotensin system may occur in response to atherosclerotic vascular injury. It is important, therefore, to provide direct proof of potential benefits of ACE inhibitors in such patients (underlining added).[4]

An article published in November of 2004 by the PEACE Trial Investigators[5] provides additional evidence that the applicability of the findings in the SOLVD and SAVE trials in patients with left ventricular dysfunction to a patient population having normal left ventricular function was "conjectural:"

> Since both of these [SOLVD and SAVE] trials were conducted in patients with impaired left ventricular function and presumed activation of the renin-angiotensin system, the applicability of these findings to populations of patients with normal left ventricular function remained conjectural.

Id. at pages 2064-2065 (underlining added).

The Examiner may argue that the clinical trials and commentary discussed above could have made it "obvious to try" those particular ACE inhibitors in patients with no evidence of left ventricular dysfunction. "Obvious to try," however, falls short of the showing needed to render the invention obvious. *In re Deuel*, 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995) (" 'Obvious to try' has long been held not to constitute obviousness"). Moreover, "direct proof" in this field was important. In this spirit, the PEACE trial itself was designed to test whether therapy with the ACE inhibitor trandolapril, when added to modern conventional therapy, would reduce the rate of nonfatal myocardial infarction, death from

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[4] Lonn et al., "Emerging Role of Angiotensin-Converting Enzyme Inhibitors in Cardiac and Vascular Protection," Circulation, vol. 90, no. 4, pp. 2056-2063 at page 2063, col. 1-2 (1994).

[5] The PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) Trial Investigators, "Angiotensin-Converting-Enzyme Inhibition in Stable Coronary Artery Disease," The New England Journal of Medicine, vol. 351, p. 2058-2068 (2004).

cardiovascular causes, or revascularization in low-risk patients with stable coronary artery disease and normal or slightly reduced left ventricular function. *Id.* at page 2059, col. 1. The authors were ultimately disappointed to report that there was no evidence of cardiovascular benefit from the addition of ACE inhibitor therapy:

> In the [PEACE Trial], 8290 patients with stable coronary artery disease and normal or near-normal left ventricular function were randomly assigned to receive trandolapril or placebo; ACE-inhibitor therapy was not found to have a significant benefit. No clinical benefit was observed in the trandolapril group despite the reduction in blood pressure in that group.

Id. at page 2065.

Although the discussion of the PEACE trial as published in the cited article does not constitute prior art, the commentary nonetheless reflects how those skilled in the art would have interpreted the SOLVD and SAVE trials, and how the results of those trials did not create an expectation of success in performing the method of the invention in a patient population having no evidence of left ventricular dysfunction, and how direct evidence of efficacy in the new patient population was important. For all the reasons explained above, the pending claims would not have been obvious in view of the cited references.

In view of these amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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